IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| In re Patent Application of:<br>Applicant: Shu-Ching Chen *et al.*<br>Serial No.: 08/900,559<br>Filed: July 25, 1997<br>For: METHODS OF USE OF ONE STEP IMMUNOCHROMATOGRAPHIC DEVICE FOR STREPTOCOCCUS A ANTIGEN | Group Art Unit: 1645<br>Examiner: Ja-Na A. Hines<br><br>I hereby certify that the documentation attached hereto is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated below and is addressed to Commissioner for Patents, Mail Stop Appeal Brief Patents, PO Box 1450, Alexandria, VA 22313-1450 on August 5, 2003 under EV 349838901 US<br>By: Kelly B. Solomon<br>Kelly B. Solomon |

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Linda 9/23/03

## APPEAL BRIEF UNDER 37 C.F.R. § 1.192

Mail Stop Appeal Brief-Patents
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal dated July 30, 2002, Appellant submits the present brief in triplicate pursuant to 37 CFR §1.192.

A check in the amount of $2,290.00 is enclosed, which includes the $320.00 fee that is required under 37 C.F.R. §§ 1.17(c) and 1.192(a) for filing a brief in support of an appeal and the $ 1,970.00 fee that is required under § 1.17(a)(5) for a five-month extension of time. If the

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accompanying payment is insufficient or additional fee is due, please charge any necessary fees to Deposit Account No. 50-2212.

Respectfully submitted,

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Contents

TABLE OF REFERENCES

## REAL PARTY IN INTEREST

The real party in interest in this appeal regarding the above-references patent application is Genzyme Corporation.

## RELATED APPEALS AND INTERFERENCES

Appellant and Appellants' counsel are not aware of any related appeals or interferences concerning this application.

## STATUS OF CLAIMS

Claims 1-9 have been cancelled.

Claims 10-21 are pending in the application. All of these claims have been finally rejected and are on appeal. A copy of the pending claims is attached as Appendix A.

## STATUS OF AMENDMENTS

Appellant has not made any amendments subsequent to final rejection of the claims made by the Examiner.

## SUMMARY OF THE INVENTION

The pending claims of the present invention relate to one-step immunoassays for the detection of Streptococcus Group A antigen (Claims 10-19) and Streptococcus antigen (Claims 20-21). *See, e.g.,* Application at p. 17, ll. 21-24. The antigen is extracted from the sample prior to running the detection assay. *See, e.g., Id.* Materials used in the methods claimed include: (1) a lateral flow immunochromatographic device that comprises a porous sample region in liquid flow contact with a separate porous detection region, which further comprises a mobile labeling reagent at a discrete labeling situs and an immobilized capture reagent at a discrete capture situs

(*see, e.g., Id.* at p. 23, ll. 6-8 and p. 37, ll. 16-21); and (2) an assay chamber which is separate from the lateral flow immunochromatographic device (*see, e.g., Id.* at p. 17, l. 24 to p. 18, l. 15 and p. 27, ll. 5-9).

The claimed methods for detecting the presence or absence of Streptococcus antigen involve extracting, within the assay chamber, the antigen from a sample by using a liquid extract made up of one or two extracting reagents. *See, e.g., Id.* at p. 18, ll. 7-10. The sample receiving region of the lateral flow immunochromatographic device is then placed into the assay chamber where it comes in contact with the liquid containing the extracted antigen. *See, e.g., Id.* at p. 18, ll. 11-15. The liquid flows from the sample receiving region to the detection region of the lateral flow immunochromatographic device passing first through a labeling situs and then to a capture situs. *See, e.g., Id.* at p. 23, ll. 9-13; p. 23, ll. 17-18; and p. 38, ll. 17-22. When the liquid arrives at the capture situs, the presence or absence of the antigen is determined. *See, e.g., Id.* at p. 38, ll. 22-25.

Other claimed methods (dependent Claim 10) further comprise the use of a control labeling situs and a control capture situs. *See, e.g., Id.* at p. 24, l. 12 to p. 25, l. 5. Still other methods of the claimed invention (dependent Claim 21) include the detection of antigens at concentrations as low as $4 \times 10^5$ cells per sample. *See, e.g., Id.* at p. 63, ll. 5-18.

## ISSUES

1. Whether Claims 10-11, 13-15, and 17-21 are patentable under 35 U.S.C. § 103 over Imrich et al. in view of Hochstrasser et al., where neither reference discloses the use of a lateral flow immunochromatographic device for the detection of Streptococcus antigen with "an assay chamber which is separate from the lateral flow immunochromatographic device," there is no suggestion to combine elements from the two references to yield the claimed invention, and evidence of secondary considerations further supports a finding of non-obviousness?

2. Whether Claims 12 and 16 are patentable under 35 U.S.C. § 103 over Imrich et al., in view of Hochstrasser et al., in view of Bogart et al., where none of the references discloses the use of a lateral flow immunochromatographic device for the detection of Streptococcus antigen with "an assay chamber which is separate from the lateral flow immunochromatographic device" where the extraction solution comprises 0.2-5M sodium nitrite and 0.02 -2M acetic acid and/or the method contains a color indicator, there is no suggestion to combine elements from the cited references to practice the claimed invention, and evidence of secondary considerations supports a finding of non-obviousness?

## GROUPING OF THE CLAIMS

The claims are characterized into five groups that, with respect to each other, **do not** stand or fall together. Reasons as to why the claims of each of these groups are separately patentable are provided in the following arguments.

Group I, consisting of Claims 10-11 and 17-20, are drawn to methods for determining the presence of Streptococcus Group A antigens (Claims 10-11 and 17-19) and Streptococcus antigens (Claim 20) comprising a lateral flow immunochromatographic device and a *separate* assay chamber. The patentability of the claims of Group I stand or fall together.

Group II, consisting of Claim 12 and Claim 13, are drawn to methods for determining the presence of Streptococcus antigens comprising a lateral flow immunochromatographic device and a *separate* assay chamber where the sample is extracted in the assay chamber for at least 10 seconds prior to inserting the lateral flow immunochromatographic device into the assay chamber. The claims in Group II are separately patentable over the claims in Groups I, III, IV and V in that the ability to extract a sample for at least 10 seconds would separately represent a new and useful improvement. The patentability of the claims of Group II stand or fall together.

Group III, consisting of Claim 14 and Claim 15, are drawn to methods for determining the presence of Streptococcus antigens comprising a lateral flow immunochromatographic device and a *separate* assay chamber where the extraction solution comprises 0.1-2.5 M sodium nitrite and 0.01-1M acetic acid (Claim 14) or 0.2-5 M sodium nitrite solution and 0.02-2 M acetic acid (Claim 15). The claims in Group III are separately patentable over the claims in Groups I, II, IV and V in that the provide specific extracting solutions which would separately represent a new and useful improvement. The patentability of the claims of Group III stand or fall together.

Group IV, consisting of Claim 16, is drawn to methods for determining the presence of Streptococcus antigens comprising a lateral flow immunochromatographic device and a *separate* assay chamber where the extraction solution comprises 2M sodium nitrite and a pH indicator and 0.3 M acetic acid. The claim in Group III is separately patentable over the claims in Groups I, II, IV and V in that the provide specific extracting solutions and a pH indicator which would separately represent a new and useful improvement.

Group V consists of dependent Claim 21 and is drawn to methods for the detection of Streptococcus cells when present in a concentration as low as $4 \times 10^5$ cells per sample. The claim in Group V is separately patentable over the claims in Groups I, II, III and IV in that the detection of Streptococcus antigen at low concentrations would separately represent a new and useful improvement.

## ARGUMENTS

### Summary

The Examiner's rejection of Claims 10-11, 13-15, and 17-21 under 35 U.S.C. § 103 over Imrich et al., in view of Hochstrasser et al. is in error. Neither Imrich et al. nor Hochstrasser et

al. disclose every element of the rejected claims, and the Examiner has failed to establish a prima facie case of obviousness by pointing to objective evidence of record that demonstrates a suggestion to combine elements from the two references to obtain the claimed invention. Moreover, Hochstrasser is from an unrelated field because it is directed to the use of chemical indicators to detect soluble analytes, not to the use of immunochromatographic devices to detect antigens that must be extracted from a sample prior to detection. Finally, even assuming arguendo that the Examiner has established a prima facie case of obviousness, the Examiner failed to properly consider evidence of secondary considerations of non-obviousness presented by the Applicants. Thus, the rejection of Claims 10-11, 13-15, and 17-21 under § 103 is improper and should be withdrawn.

The Examiner's rejection of Claims 12 and 16 under 35 U.S.C. § 103 over Imrich et al., Hochstrasser et al., and further in view of Bogart et al. is also in error. In addition to the reasons outlined above, the cited references fail to provide each limitation of the claims on appeal and the Examiner has not specifically identified a suggestion which would have motivated the artisan to modify these references to arrive at the claimed methods. Therefore, the rejection of Claims 12 and 16 under 35 U.S.C. § 103 is improper and should be withdrawn.

**The Standard for a Rejection for Obviousness Requires a Specific Showing of a Suggestion to Combine References and Consideration of Objective Evidence of Non-Obviousness**

In order for a rejection of claims under § 103 to stand, the Examiner must present evidence sufficient to establish a prima facie case of obviousness, and the Applicant must fail to rebut that prima facie case of obviousness: "To reject claims in an application under section 103,

an examiner must show an unrebutted prima facie case of obviousness." *In re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998).

The Federal Circuit recently reiterated the evidentiary burden required for the PTO to make a prima facie showing of obviousness based on the combination of elements found in multiple references. In *In re Lee*, the Federal Circuit cited with approval cases requiring specific, particular findings as to why a skilled artisan, without knowledge of the claimed invention, would have selected elements from the references to combine into the claimed invention. *In re Lee*, 277 F.3d 1338, 1343 (Fed. Cir. 2002).

> "The factual inquiry whether to combine references must be thorough and searching." *Id.* It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with.

*Id.* at 1433 (quoting *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1351-52 (Fed. Cir. 2001)). Thus, to establish a prima facie case of obviousness, the Examiner must provide a showing of a specific suggestion, teaching, or motivation to combine prior art references.

"In the absence of a proper prima facie case of obviousness, an applicant who complies with the other statutory requirements is entitled to a patent." *In re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998). As evidenced by the prosecution of the application on appeal, the Examiner has not satisfied the burden of providing an unrebutted prima facie case of obviousness and, therefore, the rejection of Claims 10-21 under 35 U.S.C. § 103 is improper and should be withdrawn.

**The Imrich et al. Reference**

Imrich et al. describe a device comprising a matrix contained within a solid casing useful for the one-step treatment and detection of analytes. *U.S. Patent No. 5,415,994* at col. 2, 18-22 and at col. 7, ll. 11-12. The device described by Imrich et al. comprises an extraction chamber; a

labeling zone; and a matrix including a sample-receiving zone and a capture zone which is used to define a flow path in fluid connection with the extraction chamber. *Id.* at col. 3, ll. 48-53.

> The extraction chamber has a sample administration port for introduction of the sample. The chamber also has an exit port through which the treated sample may flow to the sample receiving zone on the matrix.

*Id.* at col. 3, ll. 64-68. The extraction chamber is fluidly connected to the matrix by the exit port located distally in the chamber. *Id.* at col. 4, ll. 24-26. The matrix is contained within a solid casing, and the extraction chamber is formed during manufacture as an integral part of the top of the solid casing. *Id.* at col. 7, ll. 10-15. "An exit port fluidly connects the extraction chamber to the sample receiving zone." *Id.* at col. 7, ll. 10-15. The method described by Imrich et al. for detecting extracted analytes involves:

> introducing an extraction solution into the bowl portion of the extraction chamber, wherein the analyte is extracted from the sample into the extracting solution and wherein the extraction solution containing the analyte is washed onto the receiving zone of the matrix and passes through the matrix of the device . . .

*Id.* at col. 14, ll. 1-7 (emphasis added).

Inrich et al. teach away from the use of a separate preliminary step for extraction of samples, because separate extraction of samples require the user to perform time consuming and expensive "multiple" steps:

> This typically requires that the assay operator place the sample in acid and return later to transfer the acid solution to the assay medium. Multi-step assays such as these require more time and attention from health care personnel and thus are more expensive than one step assays.

*Id.* at col. 1, ll. 61-66. In fact, Imrich et al. provide a method "by which analytes requiring extraction from biological samples prior to detection may be extracted and detected in a single step. *Id.* at col. 1, ll. 8-11 (emphasis added).

**The Hochstrasser et al. Reference**

Hochstrasser et al. is not in the analogous field of lateral flow one-step immunoassays. Rather, Hochstrasser et al. is directed to a chemical indicator which requires multiple immersions in at least two different solutions in order to carry out a method to detect analyte in a sample. *See, e.g., Id.* at col. 5, l. 1 to col. 8, l. 20. The chemical indicators used by Hochstrasser et al. detect the concentration of a chemical compound in a biological solution by immersing the indicator into the solution and reading the concentration of the chemical substance directly from the instrument. *U.S. Patent No. 4,059,407* at col. 2, ll. 51-57. These immersions are not carried out to initiate lateral flow, but rather, are made to contact a titrant on the chemical indicator with the sample and/or reagent. *Id.*

The Examiner incorrectly asserts that "Hochstrasser teaches that it is well known in the art to use immersion methods to detect an antigen." Office Action dated December 11, 2002 at p. 5. However, the very general and brief disclosure that antigens are detected using the chemical indicator only applies to biological samples containing antigens which do not have to be pretreated. *Id.* at col. 7, l. 52 to col. 8, l. 20. Hochstrasser et al. do not provide any specific antigens which can be detected biological fluids using the immersion method described therein, and certainly provide no suggestion to use the labeled antigen chemical indicators for the detection of Streptococcus antigen, or any other antigen in a sample requiring pretreatment. Moreover, Hochstrasser et al. fail to provide any description of the use of labeled antibodies in the detection of any extracted antigen, let alone the Streptococcus antigen.

**The Bogart et al. Reference**

Bogart et al. describe "methods and kits for the extraction and detection of antigens from mocro-organisms using an improved extraction procedure combining a nitrous acid reagent with base or hypochlorite, or hypochlorite alone." *U.S. Patent No. 5,494,801* at col. 2, ll. 37-41. The methods described by Bogart et al. "focus on improving sample extraction so as to increase antigen availability." *Id.* at col. 2, ll. 45-47.

I. THE EXAMINER FAILED TO MEET HER INITIAL BURDEN OF FACTUALLY SUPPORTING A PRIMA FACIE SHOWING OF OBVIOUSNESS UNDER 35 U.S.C. § 103 BY FAILING TO PROVIDE A CLEAR MOTIVATION OR SUGGESTION TO COMBINE THE CITED REFERENCES TO OBTAIN THE PRESENT CLAIMED INVENTION.

"There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998) (holding that even though the references taught every element of the claimed invention, a prima facie case of obvious had not been met since there was no motivation to combine the references). Because the Examiner has failed to show any motivation to combine the cited references, none of the claims are made obvious by Imrich et al., in view of Hochstrasser et al. (Claims 10-11, 13-15 and 17-21) or by Imrich et al., in view of Hochstrasser et al., in view of Bogart et al. (Claims 12 and 16).

In rejecting Claims 10-11, 13-15 and 17-21 under 35 U.S.C. § 103 the Examiner used hindsight knowledge of the claimed invention to argue that those of skill in the art could have made modifications to the assay disclosed in Imrich et al. to obtain the claimed invention:

> [N]o more then routine skill in the art would have been required to use a device that comprises a support member, a plurality of indicating agents and separate zones comprising many of the same components as included in the device of

> Imrich, when such device is known to be useable with any biological fluid and uses a functionally equivalent method of contacting the sample with the device.

Office Action dated July 30, 2002 at p. 4. In the next Office Action, the Examiner again asserts that one of skill in the art could have incorporated the immersion technique of Hochstrasser et al. into Imrich's assay to yield the claimed invention:

> [N]o more than routine skill would have been required to incorporate the well known immersion method as taught by Hochstrasser into the method of determining the presence or absence of Streptococcus Group A antigen in a sample as taught by Imrich et al.

Office Action dated December 19, 2001 at p. 5.

Contrary to the Examiner's analysis, the test for determining whether an invention is patentable under 35 U.S.C. § 103 is not whether it takes routine skill to make a modification to the prior art. Rather, the proper test is whether one of ordinary skill in the art would have been motivated to make the modification in the first place. Here, the Examiner does not address how or why the ordinary skilled artisan would have been motivated to combine the cited references. Indeed, absent hindsight knowledge of the present invention, there is no motivation or suggestion to do so.

By looking at the level of skill required to practice the claimed invention and failing to provide the motivation or suggestion to combine the references, the Examiner improperly resorts to the use of hindsight to piece the present invention together. As the Court of Appeals for the Federal Circuit has stated:

> To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher.

*In re Fine*, 837 F.2d at 1074 (Fed. Cir. 1988) (citing *W.L. Gore Assoc. v. Garlock*, 721 F.2d 1540, 1553 (Fed. Cir. 1983)). *See also, In re Lee* at 1434 (holding that neither the examiner nor the Board adequately supported the selection and combination of the two cited references to render the claimed invention obvious) and *Interconnect Planning Corp. v. Feil*, 227 U.S.P.Q. (BNA) 543 (Fed. Cir. 1985) (holding that the district court had improperly reconstructed the claimed invention from separate components of the prior art).

Furthermore, Hochstrasser et al., which has been improperly combined by the Examiner with Imrich et al., is not from the analogous field of lateral flow one-step immunoassays and the Examiner has failed to provide any motivation or suggestion which would have led an artisan in the field of lateral flow one-step immunoassays to combine the invention of Hochstrasser et al. with the encased lateral flow immunoassay test strip described by Imrich et al. *See Teleflex Inc. v. Ficosa North America Corp.*, 63 U.S.P.Q.2d (BNA) 1374, 1387 (Fed. Cir. 2002) (holding that the jury's finding of invalidity was supported because there was no evidence of the required motivation to combine references, and the references were not clearly from analogous art).

Hochstrasser et al. also fail to provide any suggestion that its immersion technique using a chemical indicator could be useful for the detection of pretreated antigens, a limitation of Claims 10-21 of the present invention. In making her rejection, the Examiner must, therefore, be taking the position that when Hochstrasser et al. generally disclosed immersing a disposable chemical indicator into a biological solution to detect the concentration of an antigen, that the detection of any antigen by any method became obvious. This is not proper under the law as it stands. Instead, there must be some objective suggestion in the art to do what Appellant has claimed:

> In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art. In re Piasecki, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. In re Fine, 837 F.2d 1071, 1074, 5 USPQ 2d 1596, 1598 (Fed. Cir. 1988). Indeed, the teachings of the references can be combined only if there is some suggestion or incentive to do so. ACS Hospital Systems Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984).

*Ex parte Obukowicz*, 27 USPQ2d 1063, 1065, (Bd. Pat. App & Inf. 1992). This teaching or suggestion must be "clear and particular," and not merely "[b]road conclusory statements regarding the teaching of multiple references." *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999). It is inappropriate to combine art, where none of the art indicates that antigens requiring pretreatment could be detected by using an assay chamber for pre-extraction which is separate from the lateral flow immunochromatographic device used for detection.

Additionally, the Examiner has incorrectly described the disclosure of Imrich et al. when she asserts that Imrich et al. teach a physically separate chamber. Although it is true that the device described by Imrich et al. is manufactured in two plastic components—a top piece containing the sample processing feature and the bottom piece used for strip placement (*see, e.g.*, Office Action dated July 30, 2002 at pp. 2-3 and Office Action dated December 19, 2001 at p. 4)—the Examiner fails to give effect to the very next sentence where Imrich et al. state that the "top and bottom components are constructed so that a press fit secures the assembly." *U.S. Patent No. 5,145,994* at col. 7, ll. 37-41. Unlike the invention of Claims 10-21, the method of Imrich uses a test strip encased in the single casing formed from the top and bottom pieces, and the top and bottom pieces are easily or conveniently be separated once press-fit together.

The Examiner fails to provide any motivation or suggestion in the art which would have led one of ordinary skill to pry apart the two press-fit components of the Imrich et al. casing. Furthermore, Imrich et al. itself provides no suggestion to use the plastic components which make up the casing of the claimed device separately or independent of one another.

As recognized by the Examiner, although Claims 10-21 of the present invention require inserting the lateral flow immunochromatographic device into the sample chamber, Office Action dated December 19, 2001 at page 5, there is no teaching by Imrich et al. to dip the device, or any part thereof, into the sample chamber of a second device. And the Examiner has failed to point to any suggestion to do so. In fact, large devices such as the ones described by Imrich et al. are too bulky to fit within the sample chambers used in the present invention. *See* Declaration of Dr. Richard H. Schwarts at p. 5, ¶ 10.

None of the cited prior art teaches or suggests the specific "modifications" that Appellant has claimed, such as detecting Streptococcus antigen by using an assay chamber which is separate from the lateral flow immunochromatographic device. *See, e.g.,* Claims 10-21. Prior to the disclosure in the instant application, there was no suggestion to design a method whereby the lateral flow immunochromatographic device was placed into the assay chamber after extraction of the antigen. None of the cited references suggest the combination of these features; and, hence, it was not obvious to one skilled in the art to design the presently claimed methods.

In the Office Action dated July 30, 2002, the Examiner also concludes, in a cursory fashion, that one of skill in the art would have been motivated to modify the method of Imrich by using the immersion technique of Hochstrasser:

> It would have been prima facie obvious to modify the method of determining the presence or absence of Strep A antigen in a sample . . . as taught by Imrich

> wherein the modification consists of inserting the sample receiving region into a separate chamber as to allow contact of the sample as taught by Hochstrasser.

Office Action dated July 30, 2002 at page 4. This general conclusory statement does not, and cannot, satisfy the Examiner's burden to show a prima facie case of obviousness. Again, the Examiner has not provided any suggestion in the prior art of the desirability of combining the cited references to produce the claimed intention.

> When determining the patentability of a claimed invention which combines two known elements, "the question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination."

*See In re Beattie*, 974 F.2d 1309, 1311-12 (Fed.Cir.1992) (quoting *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1462 (Fed.Cir.1984)). The mere fact that a prior art device could be modified to produce the claimed device is not a basis for an obviousness rejection unless the Examiner can point to something in the prior art which suggests the desirability of such a modification. *See, e.g., In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984) (finding that there was no suggestion to turn the prior art apparatus, a liquid strainer, upside down).

The Examiner's rejection of Claims 13, 14, 15 and 21 is further improper since, in addition to failing to show any motivation or suggestion to have a separate assay chamber as discussed above, the Examiner has not provided any suggestion in the references that would have motivated the artisan to combine Imrich et al. with Hochstrasser et al. to arrive at the methods claimed. Specifically, there was no motivation in the cited references (1) to extract the sample for at least 10 seconds prior to inserting the lateral flow immunochromatographic device, as required by the claims of Group II; or (2) to have an extraction solution that comprises 0.1-2.5 M

sodium nitrite and 0.01-1M acetic acid, as required by Claim 14 of Group III or 0.2-5 M sodium nitrite solution and 0.02-2 M acetic acid, as required by Claim 15 of Group III. Furthermore, there was no suggestion to modify these references to arrive at a method which would allow for the detection of Streptococcus cells when present in a concentration as low as $4 \times 10^5$ cells per sample, as claimed by Group V.

The Examiner has also improperly combined Imrich et al., Hochstrasser et al., and Bogart et al. in rejecting Claims 12 and 16 under 35 U.S.C. § 103. Taken together, these references do not teach a method for determining the presence or absence of Streptococcus antigen, where the separate immunoassay devices and extraction chamber are provided, as described by independent Claims 10 and 20, where the extraction solution comprises 2 M sodium nitrite and 0.3 M acetic acid and a color indicator which changes color as the acetic acid is added to the sodium nitrite solution to indicate proper preparation as described in the method of Claim 16. As discussed above, Imrich et al. also fail to teach or suggest a method for the detection of an analyte where the immunoassay test strip is not in flow communication with the extraction chamber as required by independent Claims 10 and 20. Furthermore, none of these references would have motivated the artisan to modify the methods described to arrive at the invention of Claims 10-21.

Again, the Examiner has improperly used the instant invention as a template to combine the selected references. As the Federal Circuit has stated, this practice is improper for determining obviousness of an invention.

> If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such

> an approach would be "an illogical and inappropriate process by which to determine patentability."

*In re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998) (citing *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed.Cir.1996)). To prevent the use of hindsight based on the invention to defeat patentability, the examiner is required "to show a motivation to combine the references that create the case of obviousness.

To show a motivation to combine, the Examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *Id.* As discussed above, the Examiner has simply failed to meet this standard. Instead, the Examiner has merely summarized the teachings of a number of prior art references, but has failed to demonstrate a clear and particular suggestion or teaching to combine the references to lead to Appellant's claimed invention. Clearly, the detection of Streptococcus antigen by a method involving an assay chamber which is separate from the lateral flow immunochromatographic device, was not obvious, given the absence in the art of any suggestion to do so. Because the Examiner failed to demonstrate a clear and particular reason to combine the cited references, her rejection of claims 10-21 as obvious under 35 U.S.C. § 103(a) is improper and should be withdrawn.

## II. THE OBVIOUSNESS REJECTION UNDER 35 U.S.C. § 103 IS IMPROPER IN VIEW OF THE DECLARATION OF DR. RICHARD A. SCHWARTZ AND THE OBJECTIVE EVIDENCE OF NON-OBVIOUSNESS PRESENTED BY APPELLANT.

Assuming arguendo that the Examiner has met her initial burden of establishing a prima facie case of obviousness, it was improper to maintain the obviousness rejection in view of the

declaration provided by Dr. Richard A. Schwartz as well as the other evidence of non-obviousness presented by Appellant.

> Objective evidence or secondary considerations such as unexpected results, commercial success, long-felt need, failure of others, copying by others, licensing, and skepticism of experts are relevant to the issue of obviousness and must be considered in ever case in which they are present. When evidence of any of these secondary considerations is submitted, the examiner must evaluate the evidence.

MPEP 2141.01. For the reasons discussed below, the Examiner failed to afford the proper weight to the objective evidence demonstrating the advantages and improvements the claimed invention provides over the prior art and, therefore, the rejection of Claims 10-21 under 35 U.S.C. § 103 should be withdrawn.

A. The Satisfaction Of A Long-Felt Need Demonstrates Non-Obviousness Of The Invention

The methods of Claims 10-21 recite a spacial separation of the assay chamber from the lateral flow immunochromatographic assay test strip, allowing the lateral flow immunochromatographic assay test strip to be placed directly *into* the liquid extract. These improvements over the one-step immunographic assays described in the prior art provide advantages that satisfy a long-felt need in the field of "one-step" immunographic assays, e.g., by providing more convenient assays with better sensitivity. Even though Hochstrasser issued in 1977, and Imrich issued in 1995, there is no evidence of record that anyone thought to use the method taught by Hochstrasser et al. with pre-treated antigens, nor is there any evidence that anyone thought to combine Hochstrasser et al. with Imrich et al. to arrive at the claimed methods. Thus, neither reference taught or suggested the solution set forth by Applicants' for achieving more sensitive detection of an extracted Streptococcus antigen.

The claimed methods of the present invention allow for greater control over the length and efficiency of extraction, as well as the sensitivity of the assay. By separating the assay chamber from the immunochromatographic device, the user is able to determine the proper time for contacting the immunochromatographic device with the extracting solution containing the analyte. This allows the detection of Streptococcus cells at a lower concentration than the prior art devices. *See, e.g.,* Application at p. 63. For example, a device within the scope of the claim invention is able to detect Streptococcus cells when present at concentrations as low as $4 \times 10^5$ cell per sample, as compared to the one-step Quidel device which requires concentrations of at least $8 \times 10^5$ cells per sample for detection. *Id.* Claim 21 specifically includes this limitation.

In addition, Dr. Richard H. Schwartz compared the OSOM Strep A test, covered by independent Claim 10 of Appellant's application, with the QuickVue In-Line Strep A Test, described by Claim 1 of the Imrich et al. patent. Declaration of Richard H. Schwartz and Richard H. Schwartz, Pediatric Infectious Disease J., 16(11):1099-1100 (November 1997). In comparing the two tests, Dr. Richard H. Schwartz determined that the OSOM Strep A test had an overall sensitivity of 95%, while the QuickVue Strep A test had an overall sensitivity of only 87%. *Id.* at ¶ 7.

By minimizing sample manipulation following extraction, the methods of Claims 10-21 of the present invention are easier to use and require technicians with less technical experience. *See, e.g.,* Specification at 17, ll. 21-24. As explained by Dr. Richard H. Schwartz, the immunoassays used prior to the present invention required further manipulation of the sample, such as pipetting or pouring, following extraction of the sample; these manipulations introduced

additional sources of error into the test and required performance of the test by more qualified personnel:

> Other immunoassays available prior to the OSOM Strep A Test required the use of immunodiagonostic test strips in bulky housings (such as the QuickVue test and the Binax Now Strep A test) and/or required further manipulation, e.g., transfer, of the extracted sample to the immunodiagnostic test strip following sample extraction. The need for further manipulation of the extracted sample introduced additional sources of error into the tests, requiring that the tests be performed by more qualified licensed personnel.

Declaration of Richard H. Schwartz at ¶ 9. In contrast, the claimed methods of the present invention do not require such manipulation.

The Examiner has not properly considered the advantages and improvements flowing from the presently claimed invention as a whole. For those additional reasons, Claims 10-21 are patentable and the rejection under 35 U.S.C. § 103 should be withdrawn.

B. The Commercial Success Of The Claimed Invention Further Evidences Its Non-Obviousness

A finding of non-obviousness is proper where there is evidence of commercial success of a product. *See, e.g., Perkin-Elmer Corp. v. Computer Vision Corp.*, 732 F.2d 888 (Fed. Cir. 1994).

As is evident from the declaration of Dr. Richard H. Schwartz, the claimed invention has benefited from commercial success. *See* Declaration of Richard H. Schwartz. The commercial success of the OSOM product is directly related to the features of the invention, which have been incorporated into independent Claims 10 and 20, such as "providing an assay chamber which is separate from the lateral flow immunochromatographic device," and "inserting said sample receiving region of said lateral flow immunochromatographic device into said assay chamber and

contacting said liquid extract" thereby permitting more efficient extraction. *See* Declaration of Richard H. Schwartz at ¶ 4.

Thus, the Examiner has failed to give proper weight to the commercial success of the invention attributable to features of the claimed invention, as required by controlling authorities. In view of the evidence presented, the rejection of Claims 10-21 under 35 U.S.C. § 103 should therefore be withdrawn.

## CONCLUSION

For the reasons discussed above, the instant claims are not obvious in view of the cited prior art. Thus, Appellant respectfully requests that the pending rejections be withdrawn, and that the claims be allowed to issue.

Respectfully submitted,

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# APPENDIX A

Claims on Appeal

10. A method for determining the presence or absence of Streptococcus Group A antigen in a sample, comprising:

(a) providing a lateral flow immunochromatographic device comprising a sample receiving region of porous material in liquid flow contact with a separate detection region of porous material,

wherein said detection region comprises a mobile labeling reagent at a discrete labeling situs and an immobilized capture reagent at a discrete capture situs, and

wherein said labeling reagent is a detectable label coupled to a binder which specifically binds to said antigen to form a labeled complex and said capture reagent specifically binds to said antigen or to said labeled complex;

(b) providing an assay chamber which is separate from the lateral flow immunochromatographic device;

(c) extracting said antigen from said sample with an extraction solution comprising one or two extraction reagents in said assay chamber, wherein said one extraction reagent is added to the assay chamber, to form a liquid extract, or wherein said two extraction reagents are added to said assay chamber in any order, to form a liquid extract;

(d) inserting said sample receiving region of said lateral flow immunochromatographic device into said assay chamber and contacting said liquid extract whereby said liquid extract flows through said labeling situs and then through said capture situs, without further addition of reagents or manipulation of said sample; and

(e) determining the presence or absence of said antigen in said sample by detectingthe presence or absence of said detectable label at said capture situs.

11. The method of claim 10 wherein said detection region further comprises both a discrete control labeling situs comprising a mobile labeling control reagent and a discrete control capture situs comprising an immobilized control capture reagent which specifically binds to and immobilized said mobile labeling control reagent; and wherein said method further comprises:

(f) determining the presence of said immobilized control capture reagent at said control capture situs as an internal control that the assay was performed properly.

12. The method of claim 10 wherein said sample is a throat swab sample and said extracting step further comprises contacting said throat swab sample with said extraction solution in said assay chamber for at least 10 seconds.

13. The method of claim 12 wherein said sample is a throat swab sample and said extracting step further comprises vigorously mixing said throat swab in said extraction solution in said assay chamber for at least 10 seconds.

14. The method of claim 10 wherein said extraction solution comprises 0.1-2.5 M sodium nitrite and 0.01-1 M acetic acid.

15. The method of claim 10 wherein said two extraction reagents comprise a 0.2-5 M sodium nitrite solution and a 0.02-2 M acetic acid solution.

16. The method of claim 14 wherein the sodium nitrite solution comprises 2 M sodium nitrite and a pH color indicator reagent and the acetic acid solution has a concentration of 0.3 M, wherein the 0.3 M acetic acid solution is added to the 2 M sodium nitrite solution, and wherein said pH color indicator reagent changes color as the 0.3 M acetic acid solution is added to the 2 M sodium nitrite solution.

17. The method of claim 10 wherein said sample receiving region further comprises a buffer which neutralizes said liquid extract.

18. The method of claim 10 wherein the lateral flow side of said lateral flow immunochromatographic device is laminated to a backing support strip and the remaining side is not covered.

19. The method of claim 10 wherein the lateral flow side of said lateral flow immunochromatographic device is laminated to a backing support strip and the remaining side is partially covered with a strip of plastic material which allows the capture situs to be visible and so as to leave a portion of said sample receiving region exposed for inserting into said assay chamber and contacting said liquid extract.

20. A method for determining the presence or absence of Streptococcus antigen in a sample, comprising:

(a) providing a lateral flow immunochromatographic device comprising a sample receiving region of porous material in liquid flow contact with a separate detection region of porous material,

wherein said detection region comprises a mobile labeling reagent at a discrete labeling situs and an immobilized capture reagent at a discrete capture situs, and

wherein said labeling reagent is a detectable label coupled to a binder which specifically binds to said antigen to form a labeled complex and said capture reagent specifically binds to said antigen or to said labeled complex;

(b) providing an assay chamber which is separate from the lateral flow immunochromatographic device;

(c) extracting said antigen from said sample with an extraction solution comprising one or two extraction reagents in said assay chamber, wherein said one extraction reagent is added to the assay chamber, to form a liquid extract, or wherein said two extraction reagents are added to said assay chamber in any order, to form a liquid extract;

(d) inserting said sample receiving region of said lateral flow immunochromatographic device into said assay chamber and contacting said liquid extract whereby said liquid extract flows through said labeling situs and then through said capture situs, without further addition of reagents or manipulation of said sample; and

(e) determining the presence or absence of said antigen in said sample by detectingthe presence or absence of said detectable label at said capture situs.

21. The method of claim 10 or claim 20 wherein said method can detect Group A streptococcus cells when present at a concentration as low as $4 \times 10^5$ cells per said sample.